REMARKS

The present claims are claims 7-16.

The claims have been amended to conform essentially with the granted claims in the corresponding European patent. Additionally, the following preliminary remarks are provided for the Examiner's consideration.

Amended claim 7 is directed to an ophthalmological preparation that is a gel, which comprises dexamethasone dihydrogenphosphate disodium as the active agent and has a pH value above 7.3.

Such ophthalmological preparations are clearly novel in view of US 4,861,760 (Mazuel et al.) which is the reference cited in the last Office Action of May 7, 2003. Mazuel et al. discloses in Example 3 dexamethasone phosphate solutions (that may or may not turn into gels, and if so, only upon contact with the eye's liquids). There is no evidence in '760 that such later formed gels have a pH value above 7.3; in fact, their properties are not disclosed at all in '760.

The ophthalmological gel preparations according to present claim 7 are also novel in view of the other references cited in the International Search Report of May 10, 1999 as none of these documents refer specifically to ophthalmological gel formulations of dexamethasone dihydrogenphosphate disodium, at the above-mentioned pH value.

In the Office Action of May 7, 2003 the Examiner states that Mazuel et al. teach the use of dexamethasone sodium phosphate in combination with certain excipients such as mannitol, EDTA and benzalkonium chloride in a gel form for ophthalmic use.

As previously pointed out in the submission of January 28, 2002, Mazuel et al. is however concerned with ophthalmological solutions that turn into gels only upon contact with the lachrymal fluid. This behavior of the ophthalmological solutions of Mazuel et al. is due to the specific polysaccharide Gelrit®. Further, Mazuel et al. teach the use of ophthalmological solutions that turn into gels upon eye contact because they are to be administered by volumetric means (see e.g. column 2, lines 56 to 61 of US 4,861,760). In the same passage it is moreover stated that gel formulations may not be administered, e.g., by multi-dose containers.

Even if one were to accept this statement by Mazuel et al., ophthalmological solutions that turn into a gel upon eye contact have disadvantages compared to ophthalmological formulations that are gels from their initial preparation. For example, one problem commonly encountered

with ophthalmological solutions is that precipitation of the active agent takes place to a certain agree so that solutions usually have to be shaken before they are administered. If mixing of the solution is omitted, an underconcentrated solution may be applied to the eye.

In contrast, such precipitation effects occur less frequently and to a lesser degree with ophthalmological gel formulations. Therefore, the present ophthalmological gel preparations represent an advantageous alternative to the ophthalmological solutions by Mazuel et al.

As Mazuel et al. is only concerned with the aforementioned ophthalmological solutions, the gel formulations of the present application are clearly not suggested by this reference. In contract, Mazuel et al. teaches away from the gel formulations of the present invention, in that Mazuel et al. expressly requires a solution instead of a gel.

The gel formulations according to the amended claims are also not obvious in view of the other references cited by the Examiner in the previous office actions, namely US 4,271,143 (Schoenwald et al.) and US 5,252,318 (Joshi et al.).

These references merely teach ophthalmological solutions or gel formulations of dexamethasone at a slightly acidic to slightly alkaline pH, such as pH 7.1. At these pH values, irritation of the eye is reduced.

If, however, dexamethasone dihydrogen phosphate disodium is used as the active compound, one encounters the problem that at pH values around 7.0, stability is reduced so that gel formulations of this compound are not suitable for long term storage conditions as required for pharmaceutical preparations.

Attached is stability data for an ophthalmological gel preparation of dexamethasone dihydrogenphosphate disodium. Formulation A corresponds to the presently claimed invention. Formulation B is a similar formulation but the pH value was adjusted to 6.3 to 7.3. As evident from the first row, there is an unacceptable decrease in the amount of dexamethasone dihydrogenphosphate disodium of at least 14% for Formulation B. In contrast, Formulation A of the present invention exhibited only 1% decomposition of dexamethasone dihydrogenphosphate after 18 months.

The relevant data from the attached sheets is reproduced below.

Formulation A

Component	Amount (g)	Weight %
Carbopol 980	3.00	0.300
Dexamethasone-Na-Phosphate	1.107	0.1107
Cetrimide	0.100	0.0100
Na-edetate	0.100	0.0100
Sorbitol	49.00	4.900
NaOH	1.50	0.15
Water	945.193	94.5193
Total	1000.00	100%
pH Specification	7.6-8.0	

Formulation B

Component	Amount (g)	Weight %
Carbopol 980	1.5	0.30
Dexamethasone-Na-Phosphate	0.4925	0.09850
Cetrimide	0.05	0.01
Na-edetate	0.05	0.01
Sorbitol	24.50	4.900
NaOH	0.60	0.12
Water	472.8075	94.5615
Total	500.0000	100%
pH Specification	6.3-7.3	

Formulation A **Storage Conditions**

	Months	21°C/45%	25°C/60%	30°C/70%
Content (%) of Dexamethasone	0	102.0		
	3	99.0	99.8	100.1
	6	99.6	101.6	101.1
	9	102.3	101.7	101.6
	12	99.7	98.3	97.6
	18	101.3	100.9	99.1
Decomposition (%) of Dexamethasone	0	0.2		
	3	0.2	0.2	0.2
	6	0.4	0.5	0.5
	9	0.5	0.5	0.6
	12	0.5	0.6	0.7
	18	0.7	0.7	0.8

Formulation B **Storage Conditions**

	Months	21°C/45%	26°C/60%	31°C/70%
Content (%) of Dexamethasone	0	96.2		
	3	95.7	96.2	94.5
	7	95.8	94.7	92.5
	12	95.1	91.7	89.2
	18	86.3	86.0	83.9
Decomposition (%) of Dexamethasone	0			
	3	1.4	1.6	1.8
	7	2.4	2.9	3.1
	12	3.6	3.5	4.0
	18	10.7	11.2	12.9

These stability data convincingly show that if gel formulations of dexamethasone dihydrogenphosphate disodium are prepared at a pH value above 7.3, the formulations will provide for a storage stability which is required for pharmaceutical preparations.

It is submitted it was unexpected that by adjusting the pH to alkaline values, as claimed, which typically would have been considered to be irritating to the eye, ophthalmological gel compositions of dexamethasone dihydrogenphosphate disodium could be obtained that (i) are storage stable and (ii) are not irritating to the human eye. Given that such gel formulations would prevent precipitation effects as encountered with ophthalmological solutions in general, such formulations are clearly not obvious and therefore inventive in view of Mazuel et al. and the other references.

An early and favorable action on the merits is respectfully requested.

Respectfully submitted,

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